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An overview on comparative study of registration requirements for generics in US, Canada and Europe

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ABSTRACT

Generic Drug Product approval is most stringent and crucial process for company with different rules and regulation in different country. For the registration of the product company has to follow regulatory rules and requirement of country specific agency. Company should apply product marketing authorization as per norms of country requirements and should manage life cycle of that product throughout market. Need to understand and describe the various regulatory requirements for the generic drug approval process and comparison of regulated country. To understand the technical requirements required to market medicines in regulated pharmaceutical market. To evaluate similarities and differences within regulated market of U.S, Canada, and Europe. To understand and evaluate differences of post approval Changes within regulated market.

Keywords: ANDA; ANDS; EMEA; US; Canada; Europe; Regulatory Registration Requirements.

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INTRODUCTION

Generic Drug is a pharmaceutical drug product identical, pharmaceutical equivalent and Bioequivalent or comparable to reference listed drug product in dosage form safety, strength, quality, performance characteristics, and route of administration and intended use. An important factor for increasing demand of generics drug is lower as well as decline price of product which attract to customer. This generic drug product manufactures without notification or permission of innovator Drug Company after expiration of patent and exclusivity right.[2] Using bioequivalence as a tool to establish therapeutic equivalence between a reference and a generic product certainly forms the basis for market approval of multisource drug products as generic drug is a copy of branded drug. FDA detailed studied indicate that the generic drug request submitted to FDA for sanction must include the next:

- The generic drug 'pharmaceutical equivalent' to the brand.
- The 'active Ingredient' is the same as that of the brand.
- The manufacturer is capable of making the drug in correct process.
- The manufacturer is capable of making the drug consistently.
- The right amount of the ingredient effect on that part of the body on the targeted area.
- The 'inactive ingredient' of the drug is safe.
- The container in which the drug will be shipped as well as sold is appropriate.
- The label is the same as the brand-name drug's label
- Relevant patents or legal exclusivities are expired.[1]

Patent Protection of Drug

A company that developed a new drug product or drug substance should granted a patent for the drug itself, for usage for manufacturing and for method of administration and releasing the drug into blood stream. Hence a company must have more than one

Table 1: Regulation

Regulation as per agencies	US	Canada	Europe
Agency	Single Agency USFDA	1. Health Canada 2. Therapeutic Product Directorate of Health Product Food Branch. (HPFB)	Multiple Agencies 1. EMEA (European Medical Evaluation Agency) 2. National Health Agency
Registration process	Single Registration Process	Single Registration Process	Multiple Registration Process. 1. Centralized Process: (European Community) 2. Decentralized Process: (At least 2 Member State) 3. Mutual Recognition Process: (At least 2 Member State) 4. National (1Member State)
Application	Abbreviated New Drug Application (ANDA)	Abbreviated New Drug submission (ANDS)	Marketing Authorization Application (MAA)
Stability data	The Stability data for accelerated Studies are submitted for 3 Months at the time of original Submission	The Stability data for accelerated Studies are submitted for complete 6 Months at the time of original Submission	The Stability data for accelerated Studies are submitted for complete 6 Months at the time of original Submission
Approval time	18 Months	2 Years	12 Months
Pharmacopeia	US Pharmacopeia	British Pharmacopeia, European Pharmacopeia, US Pharmacopeia	British Pharmacopeia, European Pharmacopeia

Table 2: Administration requirements

Application	Form 356 (h)	HC/SC 3011	eAF Version 1.23.1.0
Agent	Required	Required	Not Required
Trend for previous submission non e-CTD)	Archival Copy –BLUE Review Copy –RED Field Copy–BURGENDY	Module: 1- RED Module, 2-YELLOW Module, 3- BLUE Module, 4- GREEN Module, 5- BLACK	Not Required
Fees	$178,799.00	$37,358.25	Different for different countries Application
Paper size for submission	Paper size (8.5 x 11) inches 11.69)inches	Paper size (8.5 x 11) inches	Paper size (8.27 x 11.69) inches
	Font 12 (New Times Roman)	Font 12 (New Times Roman)	Font 12 (New Times Roman)
	Table and Figures size i.e. 8-10	Table and Figures size i.e. 9	Table and Figures size i.e. 8-10

patent for a drug. Patent provides company to exclusive right of a drug for 20 years.[1] Usually about 10 years pass between the drug is discovered (when the patent was filed) as well as the time of drug is approved for use, exit the company only about half of the patent life to the new drug.

After a patent has expired, other company can sell as well as produce a generic version of a drug as the agency approved it. These generic drugs are sold at a lower price than the Branded drug the main reason is that the generic manufacture does not have to recover the original cost of the drug development process and hence not much spend on marketing of drug. A generic drug may be sold under its Brand name or its Generic name (A branded generic drug) but not under the brand name used by the original patent holder.

Not all expired patent drugs have generic version. sometimes it's very complex to duplicate or tests are not available to compare the generic drug acts similarly as the branded drug. Eventually the market for the Drug is so small that producing another version is not profitable.[3]

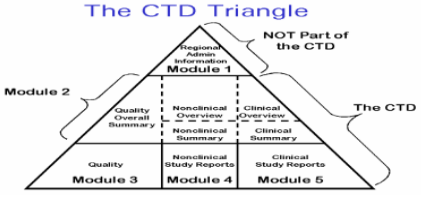

Figure 1: e-CTD Triangle

Table 3: Certifications

Regulation as per agencies	US	Canada	Europe
Environment assessment	EAS (Environment Assessment Statement) for categorical exclusion certificate in compliance with the law of EPA of US is Provided	EAS is required for new Substances in product regulated under the F& D act as per the New Substances Notification Regulations (NSN) of the Canadian Environmental Protection Act. (CEPA)	Declaration for Environmental Risk Assessment is given with the Information from GMO or Non -GMO. The fresh/New Certificate is Provided
Department Certificate	Required	Not Such Required	Not Such Required
Patent /exclusivity statement	Para I /II /III /IV	Preferred	Required
Certificate of suitability	It's Not Applicable	Preferred	Certificate of Suitability to the monograph of the European Pharmacopeia (CEP) for the European Directorates for the Quality of Medicines (EDQM) VALIDITY: 5 years.
Field copy certificate	Required Not required for biological licensing application (BLA)	Not Such Required	Not Such Required.

Table 4: Raw material controls

Regulation as per agencies	US	Canada	Europe
Definition of drug master file	A Drug Master File (DMF) is a Submission to the FDA. The main Objective is to Support regulatory requirement and to prove the quality, Safety, and efficacy.	A DMF is a reference that provides information about specific process or components used in the manufacturing processing and Packaging of a drug.	In Europe drug Master File is Known as Active Substance Master File (ASMF) or European Drug Master File (EDMF).
Type of DMF	Five Type of DMF: TYPE I: Manufacturing Site Facilities, Operating Procedure and Personnel, TYPE II: Drug Substance, Drug Substance Intermediate and Material Used in their Preparation, TYPE III: Packaging, TYPE IV: Excipient, Colorant, Flavor, Essence or Material used in their Preparation, TYPE V: FDA Acceptance Reference Information.	Four Type of DMFs: TYPEI: Substance, Drug Intermediates and Materials Used In their Preparation, TYPE II: Packaging Material, TYPE III: Colorants, Flavor and Other Additives, TYPE IV: Dosage Form.	Two Type of DMFs of: Drug Substances TYPE I : Applicant Part of DMF – Open Part.-(Non confidential), Type II: Restricted Part of DMF - Closed Part- (confidential)
Letter of Authorization	Required	Required	Required
TSE/BSE	TSE and BSE certificate are not attached in this section whereas Submitted in DMF.	TSE and BSE certificate are not attached in this section whereas Submitted in DMF.	TSE and BSE certificate are not attached in this section whereas Submitted in DMF.
Spectra Chromatogram	Required	No Such Requirement	No Such Requirement

Dossier Format: e-CTD format

- Module 1: Administrative information
- Module 2: CTD Summaries
- Module 3: Quality
- Module 4: Nonclinical study reports
- Module 5: Clinical study reports

Outline of registration requirements of US, Canada Europe

- Regulation
- Administration requirements
- Certifications
- Raw material controls

Table 5: Composition

Regulation as per agencies	US	Canada	Europe
IIG database (Inactive ingredient)	Must be within IIG Limit	No such Database Required	No such Database Required
Iron content	Maximum Daily Dose Should not be more than 5 mg / Day	No such Requirement	No such Requirement

Table 6: Manufacturing and control

Regulation as per agencies	US	Canada	Europe
Batch size	A minimum of 100,000 units OR 10% of Total Commercial production	A minimum of 100,000 units	A minimum of 100,000 units
Packaging	A minimum of 100,000 units	No Such Requirements	No Such Requirements
Number of batches (validation batches)	3	2	2

Table 7: Finished product control requirements

Regulation as per agencies	US	Canada	Europe
Justification	ICH Q(6A)	ICH Q(6A)	ICH Q(6A)
Assay	95 -105 %	95 -105 %	95 -105 %
Colour Identification	Not Required	Not Required	Required
Water contents	Required	Required	Not Required

Table 8: GMP requirements

Regulation as per agencies	US	Canada	Europe
Inspection	FDA	Health Product and Food Branch (HPFB)	MHRA /PICS/EMA
QP certification	No required	No required	Required
Clause	21 CFR Part 210 &211	Division 2, Part C of Food & Drug Regulation of HPFB	Volume 4,EU Guidelines of GMP for Medicinal Products
Import distribution site	No Such Required	Required	No Such Required

Table 9: Stability requirements

Regulation as per agencies	US	Canada	Europe
Number of batches	3	2	2
Conditions (standard for room temperature storage)	25°C 60 % RH 30°C 65 % RH 40°C 75 % RH	25°C 60 % RH 30°C 65 % RH 40°C 75 % RH	25°C 60 % RH 30°C 65 % RH 40°C 75 % RH
Data at time of Submission	6 months accelerated and 6 months long term	6 months accelerated and 6 months long term	6 months accelerated and 6 months long term
Maximum shelf life	24 Months and can be extend up to 36 Months based on Stability data	36 Months based on Stability data	36 Months based on Stability data
Container Orientation	Invert &Upright / Horizontal	Invert & Upright	Invert & Upright
Photo Stability	Light Sensitive Products	Light Sensitive Products	Light Sensitive Products

- Composition
- Manufacturing and controls
- Finished product control requirements
- Gmp requirements
- Stability requirements
- Labelling requirements
- Bioequivalence requirements
- Outside testing labs
- Post-approval requirements

Table 10: Labeling requirements

Regulation as per agencies	US	Canada	Europe
Number	NDC (10 Digit)	DIN (8 Digit)	Not Required
SPL/PLR	Required	Not Required	Not Required
Prescription Status	Rx	Pr, N	POM
Braille code	Not Required	Not Required	Required
Labels	Vial/Cartons/PI	Vial/Cartons/PI/Product Monograph	Vial/Cartons/PI/SPL
Side by side comparison	Annoted Draft Labeling (Side by Side) for label and carton compared with the RLD with Proper annotation is Provided	Annoted Draft Labeling (Side by Side) for labels and carton compared with the RLD with Proper annotation is Provided	No Annotation (Side by Side) for labeling is Provided, Labeling and Package leaflet text as per innovator to be Provided.
Packaging Insert	Packaging insert are provided for drug product in labeling	Packaging insert are provided for drug product in labeling	SPC (Summary of product characterization) is provided about drug product in labeling

Table 11: Generic drug label checkpoint of

Difference Code	US	Canada	Europe
1	Company Name / Logo	Company Name / Logo	Company Name / Logo
2	Braill Code	Drug Identification Number	Braill Code
3	Generic name	Generic name	Generic name
4	Rx/OTC Status	Rx/OTC Status	Rx/OTC Status
5	Strength	Strength	Strength
6	Pack size	Pack size	Pack size
7	Name and Address	Name and Address	Name and Address
8	Barcode	Barcode	Barcode
9	Expiry	Expiry	Expiry
10	Control/Lot No.	Control/Lot No.	Control/Lot No.
11	Label Claim	Label Claim	Label Claim
12	Storage instructions/Conditions	Storage instructions/Conditions	Storage instructions/Conditions
13	Any other text/number	Any other text/number	Any other text/number
14	-	2D Code	-

Table 12: Bioequivalence study

Regulation as per agencies	US	Canada	Europe
CRO	Audited by FDA	Audited by FDA/Health Canada	Audited by MHRA/EMEA (Medicine and Healthcare Product Regulatory Agency)
Fasting/fed state studies	Fasting or Fed/ both Depends on Product monograph	Fasting or Fed/ both Depends on Product monograph	Fasting
Analytical method validation parameters	Accuracy, precision, selectivity, sensitivity, reproducibility, calibration curve, LOQ and stability	Accuracy, precision, selectivity, sensitivity, reproducibility, calibration curve, LOQ and stability	Accuracy, precision, selectivity, sensitivity, reproducibility, calibration curve, LOQ and stability
Study dose	Made by the Manufacturer USA Reference listed drug in (Test Reference)	Made by the manufacturer Canadian reference product (Test Reference)	Made by the manufacturer European reference product. (Test Reference)
Retention of samples	5 years from the date of filing the application	No such requirement, but usually followed	No such requirement., but usually followed
Sampling points	12–18 samples, more Samples should be collected at Tmax	At least 2 samples before expected Tmax,	12–18 samples per subject/dose
Study dose	Made by the manufacturer reference listed drug in USA (Test Reference)	Made by the manufacturer reference listed drug in Canada (Test Reference)	Made by the manufacturer reference listed drug in Europe (Test Reference)

Table 13: Outside GMP labs

Regulation as per agencies	US	Canada	Europe
GDEA Certificate	Required	Not Required	Not Required
c-GLP/c-GMP Certificate	Required	Not Required	Not Required
Contractual Agreement	Not Required	Not Required	Required

Table 14: Post approval changes

Difference Code	US	Canada	Europe
Guidelines	SUPAC (Scale up and Post Approval Changes)	Supplements	Variations
Type	Post-approval changes in the approved drug: 1. Minor changes (CBE 0) 2. Moderate changes (CBE 30) 3. Major changes (Prior Approval Changes)	Post-approval changes in the approved drug: 1. Minor changes 2. Moderate changes 3. Major changes	Post-variation in the approved drug: 1. Type IA Variation (Do and tell) 2. Type IB Variation (Tell- Wait and Do Procedure) 3. Type II Variation (Major Changes)

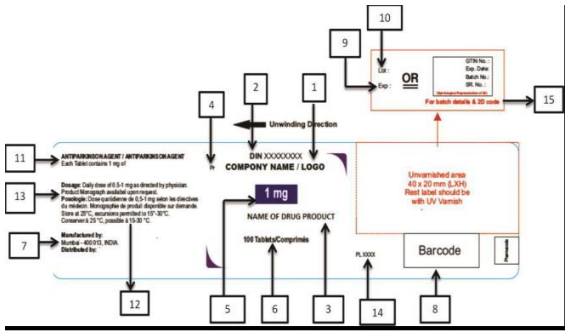

Figure 2: Generic Drug Label as per United States

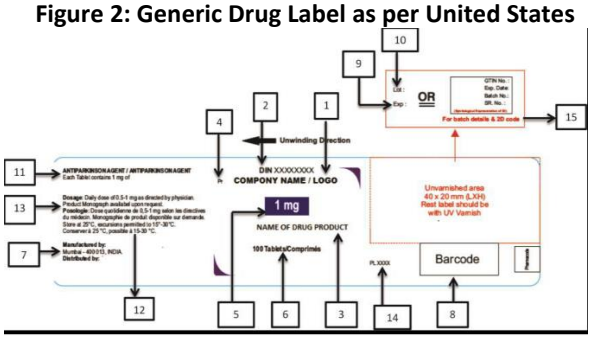

Figure 3: Generic drug label as per Canada

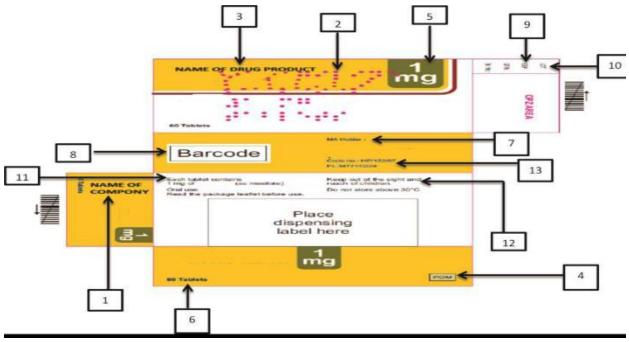

Figure 4: Generic drug label as per Europe

CONCLUSION

World Pharmaceutical market is developing very fast but regulatory profile is different for various countries. The primary purpose of the rules governing medicinal products in US, Canada, Europe is to safeguard public health. It is difficult to harmonize and switch the drug product from one country to another Regulatory rules divide world into two parts, one with regulated market like US, Japan, Europe, Australia, Canada while other is semi regulated market such as LATAM Countries, ASEAN Countries, African Countries etc. This is due to the heterogeneity in the regulatory landscape of the various countries. United State is regulated country and it has a well-developed regulation. They developed new guidance for better safety and quality with using different approaches like QbD data integrity and vigilance monitoring FDA gives new guidance day by day. It is always tuff to approved product in US market.

Canada is the 10th largest pharmaceutical market ranked in the world and second largest in North America. Continuous update in regulatory guidelines and rules makes the rules stuff and stringent for Pharma market to approved product in Canada market. The Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the low market share of generics in Europe as compared to USA and Canada.

This paper concluded specific requirements, technical Requirements, administration requirements and filling process and Bioequivalence Requirements, labeling requirements conclusion with using comparative study in between United State, Canada and Europe.

ABBREVIATIONS

ANDA: Abbreviated New Drug Application, CEPA: Canadian Environment Protection Act, CFR: Code of Federal Regulation, c-GMP: Current Good Manufacturing Practices, DIN: Drug Identification Number, DMF: Drug Master File, e-CTD: Electronic – Common Technical Document, EMEA: European Commission and the European Medicines Agency, FDA: Food and Drug Administration, GCP: Good Clinical Practices,

GLP: Good Laboratory Practices, GMP: Good Manufacturing Practices, PAS: Prior Approval Changes, QP: Quality of Product, RTR: Refuse to Receive, USFDA: United State Food and Drug Administration, USA: United State of America, WHO: World Health Organization.

REFERENCES

1. Alfonsa- Cristancho ,R. ,Andia, T., Barbosa, T., & Watanabe, J.H. Definition and Classification of Generic Drugs Across the World. Applied Health Economics and Health Policy, (2015). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC451962
2. Overview of Generic Drug.(n.d). Retrieved January20, 2017 http://msdmanuals.com/home/drugs/brand-name-and-generic-drugs/overview-of-generic-drugs-and-drug-naming
3. CDER/USFDA., Guidance for Industry ANDA Submission- Content and Format of Abbreviation New Drug Application, 2014, (June), 1-29.
4. CDER/USFDA., ANDA Filing Checklist, us-fda, 2014, 1-12.
5. CTD chart, http://uploadWikimedia.org/Wikipedia/commons/c/c2/CTD_img 004.gif.
6. Inactive Ingredient Database -FDA Update -Naiqi Ya, Acting Director for Chemistry Division IV Office of Generic Drugs Food and Drug Administration ,The USP Excipient Stackholder Forum June 18, 2014
7. http://www.fda.gov/ohrms/dockets/ac/03/slides/3968S1_02_FDA-Mele.ppt#8. (accessed June 10, 2004)
8. Available from: http://www.wikipedia.org/wiki/European_Union [Last accessed on 2012 Jan].
9. Available from: http://www.canada.ca [Last accessed on 2019 Jan].
10. Guidance for Industry Submission of Summary Bioequivalence Data for ANDAs.
11. Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products
12. Guideline on stability testing for application,ema/champ/cvmp/qwp/441071/2011_rev. 2.av ailable at: www.ema.europa.eu/docs/en_gb/document_library/seientific_guideline/2014/04/wc500164972.pdf.
13. U.S. FDA. Generic Drug User Fee Amendments (GDUFA). Retrieved Oct. 31, 2017 from https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
14. U.S. Food & Drug Administration. Abbreviated New Drug Application (ANDA). 2017. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm. Accessed 28 Nov 2017.